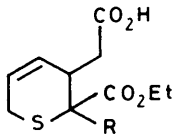
Synthetic Approaches to Thiathromboxanes. Part 2.† Synthesis of Structural Isomers of Thiathromboxane A_2

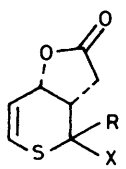
Brian P. McDonald, Robert W. Steele, James K. Sutherland,* and (in part) Bruce W. Leslie
Chemistry Department, Victoria University of Manchester, M13 9PL
Andrew Brewster
I.C.I. PLC, Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG

Structural isomers (**15**) of monothiathromboxane A2 have been prepared from the half-ester (**1**). The basic strategy involved introduction of the 'bottom' side-chain by Michael addition, lactonisation, removal of ethoxycarbonyl, and conventional introduction of the 'top' side-chain. A link with a published dithiathromboxane synthesis is described.

It is clear from Part 1 that *N*-chlorosuccinimide lactonisation of derivatives of (**1**) in the required direction necessitates that C-2 of the thiopyran ring be disubstituted. To this end we examined the reaction of (**1**) wtih $LiNPr^i_2$ to see whether a synthetically useful dianion could be obtained. Deuteriation of the species followed by exchange with H_2O gave a *cis–trans* mixture of (**2**) which, by a combination of mass spectrometry and ^1H n.m.r. spectroscopy, was shown to be *ca.* 80% monodeuteriated at C-2. Reaction of the dianion with the reactive allyl bromide gave a 69% yield of a mixture of stereoisomers of (**3**). *N*-Chlorosuccinimide–CH_2Cl_2 converted the acids (**3**) into the γ-lactones (**6**) in 79% yield. The structures followed from the characteristic pattern of spectroscopic data obtained for these compounds. In Part 1 the instability of the malonic ester (**12**) under conditions of basic hydrolysis was noted and contrasted with the stability of its dihydro derivative. The ready hydrolysis of the esters (**6**) suggested that the instability of the malonate (**12**) was associated with two electron-withdrawing groups at C-2 in addition to the double bond.



(**1**) R = H
(**2**) R = ^2H
(**3**) R = $CH_2CH{=}CH_2$
(**4**) R = $CH{=}CH(CO)(CH_2)_4Me$
(**5**) R = $CH{=}CHCH(OH)(CH_2)_4Me$



(**6**) X = CO_2Et, R = $CH_2CH{=}CH_2$
(**7**) X = CO_2H, R = $CH_2CH{=}CH_2$
(**8**) X = CO_2Et, R = $CH(CO)(CH_2)_4Me$
(**9**) X = CO_2Et, R = $CH{=}CHCH(OH)(CH_2)_4Me$
(**10**) X = CO_2H, R = $CH{=}CHCH(OH)(CH_2)_4Me$
(**11**) X = CO_2H, R = $CH{=}CHCH(OH)(CH_2)_4Me$
(**12**) X = R = CO_2Et
(**16**) X = OMe, R = $CH{=}CH(CO)(CH_2)_4Me$

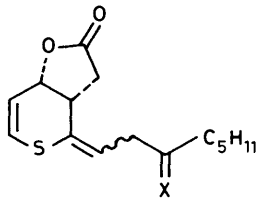
We now examined the introduction of a relevant side chain and showed that the dianion of (**1**) underwent Michael addition and elimination with (*E*)-1-chloro-oct-1-en-3-one[1] to give the enones (**4**) (60%). The structures were in accord with the spectroscopic data obtained. In addition to the typical absorptions for the thiopyran there was observed $\lambda_{max.}$ 224 nm (ε 10 000), $\nu_{max.}$ 1 680 cm^{-1}, and δ_H 6.78 and 6.45 (d, *J* 15.5 Hz) confirming the presence of an *E*-enone. Reaction of the acids (**4**) with *N*-chlorosuccinimide gave a product in good yield which could be separated into major and minor fractions. The major fraction appeared to be a single compound affording spectroscopic data in accord with γ-lactone structure (**8**), in particular the characteristic ^1H n.m.r. resonances and $\lambda_{max.}$ of the thiopyranone ring and enone unit were present. The minor fraction was not fully characterised but ^1H n.m.r. and mass spectra suggested the presence of an isomer of (**8**) and an HCl adduct to the enone double bond. Owing to the difficulty in separating the two fractions the crude product was used for further reactions. In the light of our previous experience it was no great surprise that we were unable to hydrolyse the ester (**8**) without destruction of the molecule since it has two electron-withdrawing groups in position 2. Reduction of the keto group of (**8**) with $NaBH_4$ gave the alcohols (**9**) (76%) which it was possible to hydrolyse with LiOH–H_2O–tetrahydrofuran to the acids (**10**) (91%). Oxidation of the acids (**10**) with Jones' reagent gave, after work-up, an Et_2O extract containing a polar and a non-polar fraction; heating the solution converted the polar into the non-polar component and gave a *Z*–*E* mixture of the lactones‡ (**13**). Each of the separated isomers gave i.r. and u.v. results, [$\lambda_{max.}$ 268 nm (ε 4 500) and $\nu_{max.}$ 1 725 cm^{-1}] which supported the structural assignments: similarly, the ^1H n.m.r. spectrum which, in addition to typical thiopyranofuranone resonances, showed, for the major isomer δ_H 6.07 (1 H, t, *J* 7 Hz), 3.42 (1 H, dd, *J* 19 and 7.5 Hz), and 3.22 (1 H, dd, *J* 19 and 6.5 Hz), and for the minor isomer δ_H 6.00 (1 H, t, *J* 7.5 Hz) and 3.32 (2 H, m). The mixture of isomers was used for further experiments.

Continuation of the synthesis along the planned lines required conversion of the β,γ-unsaturated ketone into the α,β-

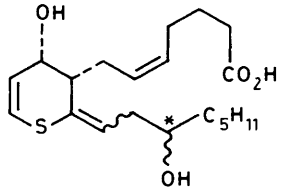
† Part 1, preceding paper.

‡ The sequence ethylene acetal formation, hydrolysis of ester, decarboxylation, hydrolysis of acetal was also investigated. The lactones (**13**) were obtained in a similar overall yield but the sequence was not as reproducible as that above.

unsaturated isomer; this we have been unable to do. Exposure of the lactones (**13**) to a variety of *O*- and *N*-centred bases gave either no change or destruction of the molecule; equally, radical-mediated isomerisations were unsuccessful as were attempts to isomerise the alcohols (**14**) with strong bases. Radical-induced decarboxylation of (**11**) was investigated without success. It is likely that the β,γ-isomer is thermodynamically more stable than the α,β in this system as in simple thio enol ethers; there, however, the equilibrium position changes dramatically in favour of the allyl isomer in going to sulphoxide and sulphone.[2]



(**13**) X = O
(**14**) X = H , OH

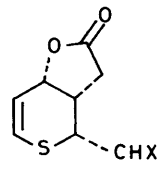


(**15**)

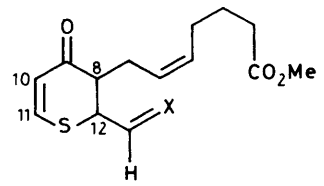
An effort to convert compound (**13**) into sulphoxide and sulphone by treatment with *m*-chloroperbenzoic acid gave only intractable mixtures. Reaction of compound (**13**) with $NaIO_4$–H_2O–MeOH did give a single product which was assigned structure (**16**) on the basis of spectroscopic data. It is likely that sulphoxidation did occur but a Pummerer-type reaction occurred subsequently.

At this stage it was thought worthwhile to introduce the 'top' side-chain into the lactone (**13**) and examine the biological activity of the product. Using conventional methodology[3] the lactones (**13**) were reduced with 2 mol of Bu^i_2AlH to give a lactol alcohol which when condensed with 3 mol equiv. of $Ph_3PCH(CH_2)_3CO_2Na$ [*ex.* $NaCH_2SOMe$ and $Ph_3\overset{+}{P}(CH_2)_4\text{-}\overset{-}{C}O_2HBr$] afforded the acids (**15**) (70%); from the method of preparation it is likely that diastereoisomers at the *atoms are present. Although we were unable to obtain satisfactory combustion analyses the ^1H n.m.r. spectrum and c.i. mass spectrum support the gross structure. Bioassays on the rabbit aorta and guinea pig ileum established that (**15**) is a weak thromboxane A_2 agonist.

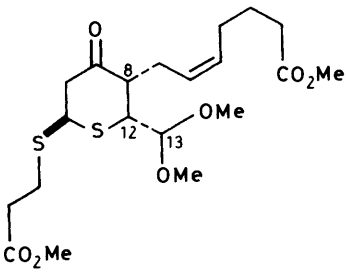
We now turned to a second strategy. Satisfactory preparations of the acetal (**17**) and the aldehyde (**18**), potential intermediates for the synthesis of dithiathromboxane A_2, were described in Part 1. Such conversions first require the introduction of the two side-chains (for which there are fairly standard methods available)[3] and, second, conversion of the dihydrothiopyran ring into the bridged thietane for which there was no established method at the inception of this stage of the project. However, during the course of the work the Ono Pharmaceutical group published[4] a synthesis of dithiathromboxane A_2 *via* the intermediates (**19T**) and (**21T**) encouraging us to investigate the synthesis of the ketone (**19T**) from the lactone (**17**). Reduction of the lactone (**17**) with Bu^i_2AlH gave a mixture of isomeric lactols (**24**) readily oxidised back to starting material with MnO_2. The lactols (**24**) were condensed with the phosphorane derived from 5-triphenylphosphoniopentanoic acid bromide using the Corey procedure to give the hydroxy acid, which was converted into the ester (**22**) with CH_2N_2. Oxidation of the ester (**22**) with CrO_3–C_5H_5N–CH_2Cl_2 gave a product which could be separated into major (81%) and minor (4%) fractions. The major fraction showed $\lambda_{max.}$ 309 nm, $\nu_{max.}$ 1 730 and 1 665 cm^{-1}, and the ^1H n.m.r. coupling pattern shown in the Figure. These results are in accord with the information provided by the Japanese workers for the isomer with *cis*-side chains (**19C**); this stereochemistry was assigned by them on the basis of the ^4J of 2



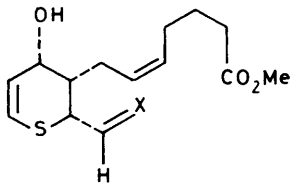
(**17**) X = (OMe)
(**18**) X = O



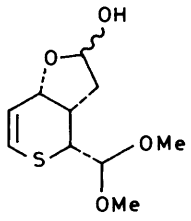
(**19**) X = $(OMe)_2$ C = R^8,R^{12} *cis*
(**20**) X = O T = R^8,R^{12} *trans*



(**21**)



(**22**) X = $(OMe)_2$
(**23**) X = O



(**24**)

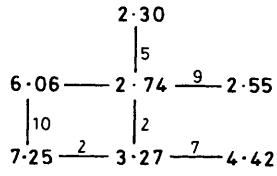


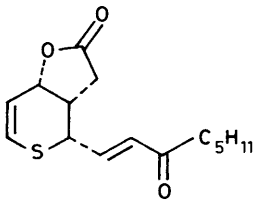
Figure.

Hz between 11-H and 12-H and is not completely unambiguous in the light of the *X*-ray structure discussed in Part 1. However, it is strengthened by the preparation of (**19C**) from the lactone (**17**) of established stereochemistry. Capillary g.l.c. showed that the major fraction contained two compounds in a 92:8 ratio. The ^1H n.m.r. spectrum did not suggest the nature of the impurity; however ^{13}C n.m.r. spectroscopy showed the expected resonances for a single isomer except for two minor absorptions at δ_C 133.4 and 127.0 suggesting that the minor component was the *E*-alkene isomer. The minor fraction which had been separated had spectroscopic data in accord with those reported for the *trans*-acetal (**19T**). Since thromboxane A_2 has the side-chains *trans* we examined the possibility of isomerising the ketone (**19C**) under a variety of equilibrating conditions. To our surprise we were unable to increase the proportion of *trans*-isomer substantially, suggesting that (**19C**) is the thermodynamically more stable isomer. This was confirmed by exchange with $NaOC^2H_3$–$^2HOC^2H_3$; ^1H n.m.r. spectroscopy demonstrated that 10-H, 8-H, and MeO had exchanged and capillary g.l.c. showed no change in isomer ratios. Attempts to change the isomer ratio by kinetic protonation of putative enolates were also unsuccessful as were attempts to isomerise the aldehyde (**20C**) which was prepared by reaction of the acetal (**19C**) with HCO_2H.[5] ^1H N.m.r. spectroscopy and reacetalis-

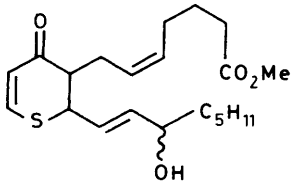
ation of the aldehyde (**20C**) confirmed that no isomerisation had occurred during the initial conversion.

The next stage of the Hamanaka synthesis involves $HSCH_2CH_2CO_2Me$ addition to the enone (**19T**) to give the sulphide (**21T**) along with a minor amount of other isomers. Addition of the thiol (catalysed by Pr^i_2NEt) to the *cis*-enone (**19C**) gave an adduct (40%) accompanied by unchanged starting material and the *cis*-enone with and *E*-alkene side-chain. The adduct which we obtained is different from that reported by the Hamanaka group; in particular in its ^1H n.m.r. spectrum 13-H is doublet δ 4.39 (*J* 2.5 Hz) coupled with a proton at δ *ca.* 2.90 as opposed to δ 4.43 (*J* 4.1 Hz) coupled to δ 3.52 (*J* 4.3 Hz). In addition, 11-H is a dd (*J* 11.5 and 3.5 Hz) at δ 4.51 in contrast to δ 4.64 (dd, *J* 8.7 and 4.7 Hz). These data do not allow an unambiguous assignment of stereochemistry to our adduct. However, the inability of $Pr^{i2}NEt$ to equilibrate the isomers (**19C**) and (**3T**) together with the regeneration of the enone (**19C**) from the adduct (**21C**) suggests that the side-chains are *cis*. ^1H N.m.r. spectroscopy indicates an equatorial sulphide substituent in (**21C**) and, provided that the acetal is pseudoaxial as in (**19C**), leads to the relative stereochemistry indicated. It follows that the Hamanaka adduct (**21T**) has *trans*- side-chains; however, the 8-H, 12-H *J* value (4.1 Hz) reported is not consistent with the diequatorial disposition of the side-chains in a chair-ring conformation.* This could be accounted for by diaxial side-chains in a chair conformation or a twist conformation. In either case, this raises the question of the sulphide stereochemistry in the Hamanaka adduct and, thus, of the thietane ring in the final dithiathromboxane-A_2. If the adduct (**21T**) has the side-chains diaxial and the sulphide equatorial then the thietane sulphur will be *trans* to the heptenoic acid side-chain. On the other hand, if the ring is a twist conformation, then either isomer is possible.

Using the aldehyde (**18**) and standard condensation with dimethyl (2-oxoheptyl)phosphonate[1] the enone (**25**) was pre-



(**25**)



(**26**)

pared. On isomerisation with $KOBu^t$–tetrahydrofuran it was converted into the β,γ-unsaturated ketone identical with the major isomer prepared as described in Part 1.

Owing to the agonist (rather than the desirable antagonist) activity reported for dithiathromboxane A_2 and the isomerisation difficulties described, these approaches were discontinued. After the completion of this work Lane and Taylor[6] showed that a more favourable *trans*–*cis* ratio of the ketones (**26C**) and (**26T**) could be obtained by NaOMe–MeOH isomerisation of (**26C**) than in the case of (**19C**). By recycling, a predominance of *trans*-adduct could be obtained. The ketone (**26C**) is potentially available from (**20C**) or (**25**).

Experimental

2-*Allyl*-3-*carboxymethyl*-2-*ethoxycarbonyl*-3,6-*dihydro*-2H-*thiopyran* (**3**).—1.4M BuLi In hexane (4.4 ml) was added to Pr^i_2NH (0.94 ml) in tetrahydrofuran (5 ml) cooled to −5 °C under a N_2 atmosphere. After 45 min the acid (**1**) (640 mg) in tetrahydrofuran (5 ml) was added slowly. The dark red solution was stirred at −10 °C for 1.5 h and then allyl bromide (0.5 ml) was added. The cooling bath was removed and after 75 min 2M HCl was added. The mixture was extracted with Et_2O (2 × 50 ml), and the extract dried, and concentrated to give an oil which after flash chromatography on silica gel eluting with $CHCl_3$–MeOH (19:1) afforded the *acids* (**3**) (520 mg) as an oil, $\nu_{max.}$ 1 730 and 1 710 cm^{-1}; δ_H 5.85 (3 H, m), 5.09 (2 H, m), 4.18 (2 H, q), 3.05 (3 H, m), 2.60 (3 H, m), 2.45 (1 H, m), and 1.24 (3 H, t) (Found: C, 57.5; H, 6.8; S, 11.9%; M^+, 270.0928. $C_{13}H_{18}O_4S$ requires C, 57.8; H, 6.7; S, 11.9%; *M*, 270.0926).

4-*Allyl*-4-*ethoxycarbonyl*-3a,7a-*dihydro*-4H-*thiopyrano*[4,3-b]*furan*-2(3H)-*one* (**6**).—*N*-Chlorosuccinimide (42 mg) was added to the acids (**3**) (82 mg) in CH_2Cl_2 (5 ml). After 90 min the solution was shaken with saturated aqueous $NaHCO_3$, dried, and concentrated to give the *lactones* (**6**) (64 mg) as an oil, $\nu_{max.}$ 1 780 and 1 725 cm^{-1}; $\lambda_{max.}$ 237 nm (ε 4 000), δ_H 6.24 (1 H, d, *J* 11 Hz), 5.75 (2 H, m), 5.14 (3 H, m), 4.21 (2 H, q), 3.24 (1 H, dt, *J* 12 and 8.5 Hz), 2.81 (2 H, m), 2.65 (1 H, dd, *J* 14.5 and 8.5 Hz), 2.48 (1 H, dd, *J* 17 and 8.5 Hz), and 1.25 (3 H, t) (Found: M^+, 268.0773. $C_{13}H_{16}O_4S$ requires *M*, 268.0769).

4-*Allyl*-4-*carboxy*-3a,7a-*dihydro*-4H-*thiopyrano*[4,3-b]*furan*-2(3H)-*one* (**7**).—LiOH (100 mg) In water (5 ml) was added to the esters (**6**) (73 mg) in tetrahydrofuran (5 ml) under a N_2 atmosphere. After 3 h 2M HCl was added and the solution saturated with NaCl and extracted with Et_2O. The extract was shaken with saturated aqueous $NaHCO_3$, acidified, and extracted with Et_2O. Concentration of the dried extracts gave the acids (**7**) (58 mg). The two acids were separated by t.l.c. on silica HF_{254} using $CHCl_3$–AcOH (4:1). The more polar product showed $\nu_{max.}$ 1 775 and 1 725 cm^{-1}; $\lambda_{max.}$ 245 nm (ε 4 300); δ_H 6.28 (1 H, dd, *J* 11 Hz), 5.84 (1 H, m), 5.79 (1 H, dd, *J* 11 and 3 Hz), 5.21 (3 H, m), 3.27 (1 H, m), and 2.75 (4 H, m) (Found: M^+, 240.0446. $C_{11}H_{12}O_4S$ requires *M*, 240.0456). The less polar product showed $\nu_{max.}$ 1 770 and 1 725 cm^{-1}; $\lambda_{max.}$ 245 nm (4 700); δ_H 6.45 (1 H, d, *J* 9 Hz), 6.19 (1 H, dd, *J* 9 and 6.5 Hz), 5.95 (1 H, m), 5.30 (2 H, m), 4.62 (1 H, d, *J* 6.5 Hz), 3.00 (1 H, dd, *J* 11 and 3.5 Hz), 2.85 (1 H, dd, *J* 17 and 4 Hz), 2.72 (1 H, dd, *J* 16 and 6 Hz), 2.57 (1 H, dd, *J* 17 and 8 Hz), and 2.36 (1 H, dd, *J* 17 and 11 Hz) (Found: M^+, 240.0454).

3-*Carboxymethyl*-2-*ethoxycarbonyl*-2-(3-*oxo*-*octenyl*)-3,6-*dihydro*-2H-*thiopyran* (**4**).—1.55M BuLi In hexane (2.75 ml) was added to Pr^i_2NH (0.6 ml) in tetrahydrofuran (5 ml) under a N_2 atmosphere at −10 °C. After 30 min the acids (**1**) (431 mg) in tetrahydrofuran (5 ml) were added to give a precipitate. After being stirred for 100 min, the mixture was cooled to −78 °C and $(Me_2N)_3PO$ (0.75 ml) added. After 1 h, 1-chloro-oct-1-en-3-one (720 mg) in tetrahydrofuran (3 ml) was added to form a dark red solution. After 3 h at −78 °C the solution was allowed to warm to ambient temperature overnight. 2M HCl Was added and the solution extracted with Et_2O (3 × 30 ml). The extract was repeatedly shaken with saturated aqueous Na_2CO_3 until the water was no longer red. The basic extracts were acidified with 2M HCl and shaken with EtOAc. After being shaken with saturated brine the dried EtOAc solution was concentrated to give a red oil which on flash chromatography on silica gel eluting with hexane–Et_2O–HCO_2H (15:15:2) gave the *enones* (**4**) (497 mg) as an oil, $\nu_{max.}$ 1 735, 1 710, and 1 680 cm^{-1}; $\lambda_{max.}$ 224 nm (10 000); δ_H 6.78 (1 H, d, *J* 15.5 Hz), 6.45 (1 H, d, *J* 15.5 Hz), 5.96 (1 H, m), 5.81 (1 H, m), 4.23 (2 H, q), 3.19 (1 H, m), 3.03 (2 H, br s), 2.60 (4 H, m), 1.68 (2 H, m), 1.26 (6 H, m), and 0.86 (3 H, t). A 2,4-dinitrophenylhydrazone of the methyl ester of (**8**) was prepared, m.p. 98—101 °C (Found: C, 54.7; H, 5.9; N,

* The mirror enone which we obtained substantially agrees with the ^1H n.m.r. data reported for the enone (**3T**) except that 10-H and 8-H show long-range coupling of 2 Hz. If these compounds are indeed identical then the ring system cannot have the assumed half-chair conformation.

10.2; S, 5.8. $C_{25}H_{32}N_4O_8S$ requires C, 54.7; H, 5.9; N, 10.2; S, 5.8%).

4-*Ethoxycarbonyl*-4-(3-*oxo-octenyl*)-3a,7a-*dihydro*-4H-*thiapyrano*[4,3-b]*furan*-2(3H)-*one* (**8**).—*N*-Chlorosuccinimide (58 mg) was added to the acids (**4**) (138 mg) in CH_2Cl_2 (5 ml). After 1 h, insoluble material was filtered off and the solvent removed under reduced pressure. The residue was dissolved in Et_2O, and the solution shaken with saturated aqueous $NaHCO_3$, dried, and concentrated to give the *lactones* (**8**) (120 mg), $\nu_{max.}$ 1 795, 1 740, 1 705, 1 685, and 1 620 cm^{-1}; $\lambda_{max.}$ 222 nm (ε 10 000), δ_H 6.82 (1 H, d, *J* 15.5 Hz), 6.49 (1 H, d, *J* 15.5 Hz), 6.24 (1 H, d, *J* 11 Hz), 5.78 (1 H, dd, *J* 11 and 3 Hz), 5.06 (1 H, dd, *J* 8 and 3 Hz), 5.73 (2 H, m), 3.43 (1 H, dt, *J* 12 and 8 Hz), 2.89 (1 H, dd, *J* 17.5 and 12 Hz), 2.60 (1 H, dd, *J* 17.5 and 8 Hz), 2.52 (2 H, br t), 1.58 (2 H, m), 1.28 (4 H, m), and 0.86 (3 H, t). (Found: M^+, 352.1344. $C_{18}H_{24}O_5S$ requires *M*, 352.1344).

4-*Ethoxycarbonyl*-4-(3-*hydroxyoctenyl*)-3a,7a-*dihydro*-4H-*thiopyrano*[4,3-b]*furan*-2(3H)-*one* (**9**).—$NaBH_4$ (5 mg) Was added to the enones (**8**) (88 mg) in water (2 ml) and EtOH (4 ml). After 30 min, 2M HCl was added and the solution saturated with NaCl and then extracted with EtOAc. Concentration of the dried extract gave an oil which was flash chromatographed on silica gel eluting with hexane–EtOAc (1:1) to give the *alcohols* (**9**) (57 mg), $\nu_{max.}$ 3 500, 1 785, and 1 735 cm^{-1}; $\lambda_{max.}$ 235 nm (ε 5 200); δ_H 6.24 (1 H, d, *J* 10.5 Hz), 6.05 (1 H, ddd, *J* 15.5, 5.5, and 3 Hz), 5.83 (1 H, d, *J* 15.5 Hz), 5.74 (1 H, dd, *J* 10.5 and 3 Hz), 5.07 (1 H, dd, *J* 8 and 3 Hz), 5.76 (2 H, q, *J* 7 Hz), 4.19 (1 H, m), 3.39 (1 H, dt, *J* 12 and 8 Hz), 2.87 (1 H, dd, *J* 17 and 12 Hz), 2.57 (1 H, ddd, *J* 17, 8, and 2 Hz), 1.68 (1 H, m), 1.52 (2 H, m), 1.28 (9 H, m), and 0.87 (3 H, t, *J* 7 Hz); *m/z* (c.i., NH_3) 372, 355, and 337.

On oxidation with MnO_2–CCl_4, the alcohols (**9**) were converted back into enones.

4-(3-*Oxo-octylidene*)-3a,7a-*dihydro*-4H-*thiopyrano*[4,3-b]-*furan*-2(3H)-*one* (**13**).—The alcohols (**9**) (64 mg) were dissolved in tetrahydrofuran (3 ml) and LiOH (50 mg) in water (2 ml) was added. After 14 h, the red solution was acidified with 2M HCl, saturated with NaCl, and extracted with Et_2O. The ether extracts were shaken with saturated aqueous Na_2CO_3, the basic extract acidified with 2M HCl and the solution extracted with Et_2O. Drying and concentration of the Et_2O solution gave the *acids* (**10**) (54 mg); δ_H 6.38 (1 H, d, *J* 10.5 Hz), 6.11 (1 H, dd, *J* 15 and 5.5 Hz), 5.93 (1 H, d, *J* 15 Hz), 5.71 (1 H, dd, *J* 10.5 and 3 Hz), and 5.14 (1 H, dt, *J* 8 and 3 Hz).

Jones' reagent was added dropwise to the acids (**10**) (250 mg) in Me_2CO (15 ml) at 0 °C until t.l.c. indicated disappearance of starting material. The mixture was filtered and the filtrate concentrated under reduced pressure, diluted with Et_2O, and the solution shaken with 2M HCl. T.l.c. showed one major component. The solution was heated under reflux for 2 h by which time the major product had been transformed into another. Concentration gave the *ketones* (**13**) (111 mg) as an oil, $\nu_{max.}$ 1 795 and 1 725 cm^{-1}; $\lambda_{max.}$ 268 nm (ε 4 500). The two isomers could be separated by t.l.c. [4 elutions with hexane–EtOAc (3:1)]. The more polar isomer was the major component, δ_H 6.21 (1 H, d, *J* 10.5 Hz), 6.07 (1 H, t, *J* 6.5 Hz), 5.75 (1 H, dd, *J* 10.5 and 2.5 Hz), 5.13 (1 H, dd, *J* 8 and 3 Hz), 3.59 (1 H, dt, *J* 12.5 and 8 Hz), 3.42 (1 H, dd, *J* 19 and 7.5 Hz), 3.22 (1 H, dd, *J* 18.5 and 6 Hz), 2.90 (1 H, dd, *J* 17.5 and 12.5 Hz), 2.53 (1 H, dd, *J* 17.5 and 8 Hz), 2.42 (1 H, t, *J* 7.5 Hz), 1.56 (2 H, m), 1.24 (4 H, m), and 0.87 (3 H, t, *J* 7 Hz) (Found: M^+, 280.1132. $C_{15}H_{20}O_3S$ requires *M*, 280.1133). The minor component showed δ_H 6.25 (1 H, d, *J* 10 Hz), 6.00 (1 H, t, *J* 7.5 Hz), 5.71 (1 H, dd, *J* 10.5 and 2.5 Hz), 5.11 (1 H, br d, *J* 8 Hz), 3.77 (1 H, dt, *J* 12.5 and 8 Hz), 3.32 (2 H, m), 2.92 (1 H, dd, *J* 17.5 and 12.5 Hz), 2.52 (1 H, dd, *J* 17 and 8 Hz), 2.45 (2 H, t, *J* 7 Hz), 1.53 (2 H, m), 1.23 (4 H, m), and 0.87 (3 H, t, *J* 7 Hz) (Found: M^+, 280.1126. $C_{15}H_{20}O_3S$ requires *M*, 280.1133).

Oxidation of the Enones (**13**).—$NaIO_4$ (27 mg) Was added to the enones (**13**) (27 mg) in water (2 ml) and MeOH (1 ml). After 3 days the mixture was filtered and the filtrate saturated with NaCl and extracted with EtOAc. Concentration of the dried extract gave the *ether* (**16**) (13 mg) after purification by flash chromatography on silica gel eluting with pentane–Et_2O (1:1), $\nu_{max.}$ 1 790, 1 750, and 1 625 cm^{-1}; $\lambda_{max.}$ 222 nm (ε 9 100); δ_H 6.60 (1 H, d, *J* 16 Hz), 6.41 (1 H, d, *J* 16 Hz), 6.16 (1 H, d, *J* 10.5 Hz), 5.89 (1 H, dd, *J* 10.5 and 3 Hz), 5.26 (1 H, dd, *J* 7.5 and 3 Hz), 3.34 (3 H, s), 3.02 (1 H, dt, *J* 12.5 and 8 Hz), 2.81 (1 H, dd, *J* 17 and 12.5 Hz), 2.56 (1 H, t, *J* 7 Hz), 2.38 (1 H, dd, *J* 17 and 8 Hz), 1.61 (2 H, m), 1.30 (4 H, m), and 0.89 (3 H, t, *J* 7 Hz) (Found: M^+, 310.1239. $C_{16}H_{22}O_4S$ requires *M*, 310.1239).

Reduction of the Enones (**13**).—$NaBH_4$ (21 mg) Was added to the enones (**13**) (122 mg) in EtOH (4 ml) and water (2 ml). After 1 h, 2M HCl was added and the solution saturated with NaCl and extracted with EtOAc. Concentration of the dried extracts and flash chromatography (pentane–EtOAc, 2:1) of the product gave the minor *alcohol* (**14**) (20 mg), $\nu_{max.}$ 1 775 cm^{-1}; $\lambda_{max.}$ 268 (ε 6 400), δ_H 6.23 (1 H, d, *J* 10.5 Hz), 5.92 (1 H, td, *J* 8 and 2 Hz), 5.69 (1 H, dd, *J* 10.5 and 2.5 Hz), 5.07 (1 H, dm, *J* 13 Hz), 3.92 (1 H, m), 3.66 (1 H, m), 2.90 (1 H, dd, *J* 17 and 13 Hz), and 2.65—0.88 (14 H) (Found: M^+, 282.1292. $C_{15}H_{22}O_3S$ requires *M*, 282.1290) and the major *alcohol* (**14**) (69 mg), $\nu_{max.}$ 1 775 cm^{-1}; $\lambda_{max.}$ 266 nm (ε 6 200); δ_H 6.23 (1 H, d, *J* 10.5 Hz), 5.93 (1 H, m), 5.72 (1 H, dd, *J* 10.5 and 2.5 Hz), 5.02 (1 H, dm, *J* 7.5 Hz), 3.71 (1 H, m), 3.55 (1 H, dt, *J* 12.5 and 7.5 Hz), 2.90 (1 H, ddd, *J* 17.5, 12.5, and 2 Hz), 2.52 (1 H, dd, *J* 17.5 and 8 Hz), and 7.5—0.9 (15 H); *m/z* (c.i., NH_3) 300.283.

Oxidation of the separated alcohols with Jones' reagent gave single isomers of the enone (**13**) identical with those prepared previously.

(Z)-6-[4-*Hydroxy*-3-(3-*hydroxyoctylidene*)-3,4-*dihydro*-2H-*thiopyran*-1-*yl*]*hept*-5-*enoic Acid* (**15**).—Bu^i_2AlH In hexane (1M solution; 1.4 ml) was added to the enones (**13**) (177 mg) in PhMe (20 ml) cooled to −78 °C under a N_2 atmosphere. After 3 h water (2 ml) was added and the cooling bath removed. 2M HCl Was added, the solution saturated with NaCl, and the solution extracted with Et_2O to give, after drying and concentration of the extract, the *lactol* (161 mg).

NaH (50% Dispersion in oil; 1 g) was washed with pentane under a N_2 atmosphere. Me_2SO (20 ml) was added and the stirred suspension warmed, the temperature being kept below 60 °C. After 4 h evolution of H_2 had ceased and the solution was cooled to ambient temperature. 5-Triphenylphosphoniopentanoic acid bromide (880 mg) and Me_2SO (5 ml) were stirred together and the 'dimsyl sodium' solution prepared above added dropwise (4.2 ml) to give a red solution of the ylide. The lactol (138 mg) in Me_2SO (3 ml) was added to the ylide solution. After 12 h water was added and the solution extracted with EtOAc. The aqueous layer was taken to pH 6 with 2M HCl and shaken with EtOAc. Drying and concentration of the latter extract gave an oil which was flash chromatographed on silica gel eluting with EtOAc to give the *acids* (**15**) (137 mg), $\nu_{max.}$ 1 710 cm^{-1}; δ_H 6.12 (1 H, d, *J* 10 Hz), 5.83 (1 H, dm, *J* 10 Hz), 5.63 (1 H, t, *J* 8 Hz), 5.44 (2 H, m), 4.78 (2 H, br s), 4.39 (1 H, m), 3.71 (1 H, m), and 2.70—0.9 (22 H, m); *m/z* (c.i., NH_3) 386, 367, 351, and 319.

4-(*Dimethoxymethyl*)-2,3,3a,7a-*tetrahydro*-4H-*thiopyrano*-[4,3-b]*furan*-2-*ol* (**24**).—1.2M Bu^i_2AlH In hexane (1.45 ml) was added to the lactone (**17**) (200 mg) in PhMe (20 ml) at −78 °C

under a N_2 atmosphere. After 2 h, saturated aqueous Na_2SO_4 (2 ml) was added and the cooling bath removed. Na_2SO_4 Was added, the mixture filtered, and the residue washed with EtOAc. The dried extracts were filtered through a plug of silica gel and the silica gel eluted with Me_2CO. Concentration of the eluates gave a 4:3 mixture of *lactols* (**24**) (174 mg), δ_H 6.18 and 6.14 (d, *J* 10.5 Hz), 5.89 and 5.81 (dd, *J* 10.5 and 3 Hz), 5.52 (d, *J* 5 Hz), and 4.45 and 4.44 (d, *J* 5.5 Hz) (Found: M^+, 232.0766. $C_{10}H_{16}O_4S$ required *M*, 232.0769).

On oxidation with MnO_2–CH_2Cl_2 the lactols (**24**) were converted into the lactone (**1**) in high yield.

Methyl (Z)-6-[2-*Dimethoxymethyl*-3-*hydroxy*-3,4-*dihydro*-2H-*thiopyran*-2-*yl*]*hept*-5-*enoate* (**22**).—A 60% dispersion of NaH (225 mg) was washed with pentane under a N_2 atmosphere. Me_2SO (6.5 ml) Was added and the mixture heated at 65 °C for 45 min. The solution was cooled to ambient temperature and 5-triphenylphosphoniopentanoic acid bromide (1.24 g) in Me_2SO (3.5 ml) was added. The mixture was then stirred at ambient temperature for 45 min after which the lactols (**24**) (216 mg) in Me_2SO (3 ml) were added. After 2.5 h, water (250 ml) was added and the solution saturated with NaCl and extracted with Et_2O (100 ml). The aqueous phase was acidified to pH 4 with 2M HCl and extracted with Et_2O (4 × 100 ml). The dried extracts were concentrated and the residue triturated with EtOAc and the solid (Ph_3PO) filtered off. The filtrate was concentrated and Et_2O (20 ml) added followed by CH_2N_2–Et_2O until esterification was complete. After removal of solvent the residue was flash chromatographed on silica gel eluting with pentane–Et_2O to give the *ester* (**22**) (222 mg) as an oil, $\nu_{max.}$ 1 725 cm^{-1}; $\lambda_{max.}$ 229 nm (ε 4 000); δ_H (1 H, dd, *J* 10.2 and 1 Hz), 5.69 (1 H, dd, *J* 10.2 and 2.4 Hz), 5.45 (2 H, dm, *J* 8.5 Hz), 4.42 (1 H, s, *J* 7.5 Hz), 4.34 (1 H, m), 3.63 (3 H, s), 3.41 (3 H, s), 3.32 (3 H, s), 3.18 (1 H, dd, *J* 7.5 and 4.5 Hz), 2.28 (2 H, t, *J* 6 Hz), 2.3 (5 H, m), and 1.65 (2 H, m) (Found: M^+, 329.1419. $C_{16}H_{25}O_5S$ requires *M*, 329.1423).

Methyl (Z)-6-(2-*Dimethoxymethyl*-3-*oxo*-3,4-*dihydro*-2H-*thiopyran*-2-*yl*)*hept*-5-*enoate* (**19C**).—The alcohol (**22**) (220 mg) in CH_2Cl_2 (5 ml) at −20 °C was treated with Collins' reagent (10 ml). After 35 min the mixture was diluted with Et_2O (100 ml) and successively washed with 1M NaOH (2 × 50 ml), 1M HCl (2 × 20 ml), and saturated brine (25 ml). The dried extract was concentrated and the residue flash-chromatographed on silica gel eluting with pentane–Et_2O to give the cis-*ketone* (**19C**) (177 mg), $\nu_{max.}$ 1 730 and 1 665 cm^{-1}; $\lambda_{max.}$ 309 nm; δ_H 7.25 (1 H, dd, *J* 10 and 2 Hz), 6.06 (1 H, d, *J* 10 Hz), 5.52 (1 H, m), 5.40 (1 H, m), 4.42 (1 H, d, *J* 7 Hz), 3.64 (3 H, s), 3.40 (3 H, s), 3.35 (3 H, s), 3.27 (1 H, ddd, *J* 7, 2, and 2 Hz), 2.74 (1 H, m), 2.55 (1 H, m), 2.30 (3 H, t, *J* 6.5 Hz), 2.11 (2 H, q, *J* 6.5 Hz), and 1.67 (2 H, m); δ_C 195.37 (s), 173.900 (s), 143.02 (d), 132.47 (d), 126.33 (d), 121.95 (d), 104.23 (d), 55.79 (q), 55.28 (q), 51.49 (q), 47.82 (d), 45.77 (d), 33.42 (t), 27.4 (t), 26.66 (t), 24.71 (t), 26.66 (t), and 24.71 (t). In addition, there were minor resonances at 133.37 and 126.95 for the *E*-alkene (*ca.* 7%) (Found: M^+, 328.1345. $C_{16}H_{24}O_5S$ requires *M*, 328.1344).

The *trans*-ketone (**19T**) (9 mg) was also isolated; δ_H 7.35 (1 H, d, *J* 10 Hz), 6.07 (1 H, dd, *J* 10 and 2 Hz), 5.34 (2 H, m), 4.67 (1 H, d, *J* 8 Hz), 3.87 (1 H, m), 3.65 (3 H, s), 3.36 (3 H, s), 3.35 (3 H, s), 2.74 (1 H, m), 2.42 (2 H, m), 2.28 (2 H, m), 2.05 (2 H, m), and 1.67 (2 H, m).

Methyl (Z)-6-(2-*Formyl*-3-*oxo*-3,4-*dihydro*-2H-*thiopyran*-2-*yl*)*hept*-5-*enoate* (**20C**).—Freshly distilled formic acid (1 ml) was added to the acetal (**19C**) (71 mg) in CH_2Cl_2 (2 ml). After 3 h, CH_2Cl_2 (40 ml) was added and the solution shaken with saturated aqueous $NaHCO_3$ and then saturated brine. The dried CH_2Cl solution was concentrated to give an oil which was flash chromatographed eluting with pentane–Et_2O to give the *aldehyde* (**20C**) (41 mg); $\nu_{max.}$ 1 725 and 1 665 cm^{-1}; δ_H 9.63 (1 H, s), 7.09 (1 H, dd, *J* 10.5 and 2 Hz), 6.12 (1 H, d, *J* 10.5 Hz), 5.58 (1 H, m), 5.39 (1 H, m), 3.78 (1 H, m), 3.66 (3 H, s), 2.86 (1 H, m), 2.58 (1 H, m), 2.31 (3 H, m), 2.10 (2 H, m), and 1.69 (2 H, m); *m/z* (c.i., NH_3) 300, 283.

Reaction of the aldehyde (**20C**) with $SmCl_3$–$8H_2O$–$HC(OMe)_3$–MeOH regenerated the acetal (**19C**).

3-*Mercaptopropionate Adduct of the Acetal* (**19C**).—Methyl 3-mercaptopropionate (87 μl) and Pr^i_2NEt (9 μl) were added to the ketone (**19C**) (86 mg) in Me_2NCHO (1.4 ml). After 14 h, concentration under reduced pressure gave an oil which was flash chromatographed on silica gel eluting with pentane–Et_2O to give the *adduct* (**21C**) (46 mg); $\nu_{max.}$ 1 730 and 1 705 cm^{-1}; δ_H 5.49 (1 H, m), 5.30 (1 H, m), 4.51 (1 H, dd, *J* 11.5 and 3 Hz), 4.39 (1 H, d, *J* 2.5 Hz), 3.67 (3 H, s), 3.64 (3 H, s), 3.40 (3 H, s), 3.36 (3 H, s), 2.90 (3 H, m), 2.60 (6 H, m), 2.27 (3 H, t, *J* 7 Hz), 2.07 (2 H, m), and 1.64 (2 H, m) (Found: M^+, 448.1591. $C_{20}H_{32}O_7S_2$ requires *M*, 448.1589). The other fraction isolated was (as judged by ^1H n.m.r. spectroscopy) a 2:1 mixture of starting material and a compound showing δ_H 4.65 (d, *J* 6 Hz), 4.31 (m), 3.63, 3.34, 3.33, and 3.13 (all s).

4-[(E)-3-*Oxo*-*octenyl*]-3a,7a-*dihydro*-4H-*thiopyrano*[4,3-b]-*furan*-2(3H)-*one* (**25**).—Dimethyl (2-oxoheptyl)phosphonate (76 μl) in $(MeOCH_2)_2$ (1 ml) was added to NaH (50% dispersion in oil; 16 mg) in $(MeOCH_2)_2$ (1 ml) under a N_2 atmosphere. After 10 min, the aldehyde (**18**) (60 mg) in $(MeOCH_2)_2$ (4 ml) was added. After 30 min, water (10 ml) was added and the solution extracted with Et_2O (10 ml). The Et_2O solution was separated off, shaken with saturated brine, dried, and concentrated to give an oil. Chromatography of this on silica gel gave the *enone* (**25**) (50 mg), $\nu_{max.}$ 1 770 and 1 700 cm^{-1}; $\lambda_{max.}$ 223 nm (ε 12 000); δ_H 6.82 (1 H, dd, *J* 15 and 6 Hz), 6.34 (1 H, d, *J* 15 Hz), 6.24 (1 H, d, *J* 10.5 Hz), 5.78 (1 H, dd, *J* 10.5 and 3 Hz), 5.06 (1 H, dd, *J* 8 and 3 Hz), 3.54 (1 H, d, *J* 3 Hz), 3.16 (1 H, m), 2.89 (1 H, dd, *J* 17 and 12 Hz), 2.60 (1 H, dd, *J* 17 and 8 Hz), 2.52 (2 H, t, *J* 7 Hz), 1.68 (2 H, m), 1.28 (4 H, m), and 0.86 (3 H, t, *J* 7 Hz) (Found: M^+, 280.1132. $C_{15}H_{20}O_3S$ requires *M*, 280.1133).

The enone (**25**) (35 mg) was added to $KOBu^t$ (1 mg) in tetrahydrofuran (1 ml) and the red solution was stirred for 3 h. Water (5 ml) was added and the solution extracted with Et_2O (5 ml). The dried extract was concentrated to give an oil which was flash chromatographed to give the β,γ-unsaturated ketone (18 mg), which was identical with the major isomer prepared as described in Part 1.

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